COMPOUNDS

The present invention relates to certain heterocyclic compounds, processes and intermediates used in their preparation, pharmaceutical compositions containing them and their use in therapy.

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved cysteine motif. At the present time, the chemokine superfamily comprises four groups exhibiting characteristic structural motifs, the C-X-C, C-C and C-X_3-C and XC families. The C-X-C and C-C families have sequence similarity and are distinguished from one another on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues. The C-X_3-C family is distinguished from the other two families on the basis of having a triple amino acid insertion between the NH-proximal pair of cysteine residues. In contrast, members of the XC family lack one of the first two cysteine residues.

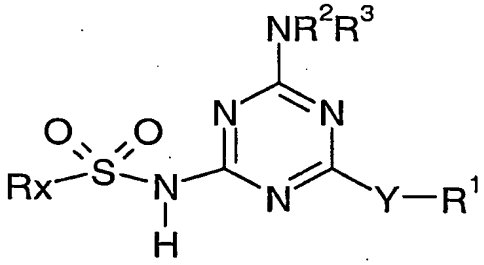
The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils. Examples include human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

The C-X_3-C chemokine (also known as fractalkine) is a potent chemoattractant and activator of microglia in the central nervous system (CNS) as well as of monocytes, T cells, NK cells and mast cells.

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX_3CR1 for the C-X_3-C family. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

The present invention provides compounds of formula (1), a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof:



(1)

wherein Y is selected from a bond, -S-, -O-, -NR^5-, -CF_2-CH_2-, -CF_2CF_2-, -$CONR^5$- , phenyl or heteroaryl;

wherein R^1 is a group selected from C_{3-7}carbocyclyl, C_{1-8}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl; wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from fluoro, nitrile, -OR^4, -NR^5R^6, -$CONR^5R^6$, -$COOR^7$, -NR^8COR^9, -SR^{10}, -SO_2R^{10}, -$SO_2NR^5R^6$, -$NR^8SO_2R^9$, phenyl or heteroaryl; wherein phenyl and heteroaryl are optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, -OR^4, -NR^5R^6, -$CONR^5R^6$, -$COOR^7$, -NR^8COR^9, -SR^{10}, -SO_2R^{10}, -$SO_2NR^5R^6$, -$NR^8SO_2R^9$, C_{1-6}alkyl and trifluoromethyl;

wherein R^2 is C_{3-7}carbocyclyl, optionally substituted by 1, 2 or 3 substituents independently selected from fluoro, -OR^4, -NR^5R^6 -$CONR^5R^6$, -$COOR^7$, -NR^8COR^9, -SR^{10}, -SO_2R^{10}, -$SO_2NR^5R^6$, -$NR^8SO_2R^9$;

or R^2 is a 3-8 membered ring optionally containing 1, 2 or 3 atoms selected from O, S, -NR^8 and whereby the ring is optionally substituted by C_{1-3}alkyl or fluoro;

or R^2 is a phenyl or heteroaryl, each of which is optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, -OR^4, -NR^5R^6, -$CONR^5R^6$, -NR^8COR^9, -$SO_2NR^5R^6$, -$NR^8SO_2R^9$, C_{1-6}alkyl and trifluoromethyl;

or R^2 is a group selected from C_{1-8}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl wherein the group is substituted by 1, 2 or 3 substituents independently selected from hydroxy, amino, C_{1-6}alkoxy, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, *N*-(C_{1-6}alkyl)-*N*–(phenyl)amino, *N*-C_{1-6}alkylcarbamoyl, *N,N*-di(C_{1-6}alkyl)carbamoyl, *N*-(C_{1-6}alkyl)-*N*–(phenyl)carbamoyl, carboxy, phenoxycarbonyl, –NR^8COR^9, –SO_2R^{10}, –$SO_2NR^5R^6$ and –$NR^8SO_2R^9$;

wherein R^3 is hydrogen or independently R^2;

R^4 is hydrogen or a group selected from C_{1-6}alkyl and phenyl, wherein the group is optionally substituted by 1 or 2 substituents independently selected from halo, phenyl, $-OR^{11}$ and $-NR^{12}R^{13}$;

R^5 and R^6 are independently hydrogen or a group selected from C_{1-6}alkyl and phenyl wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, phenyl, $-OR^{14}$,$-NR^{15}R^{16}$, $-COOR^{14}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-SO_2R^{10}$, $-SONR^{15}R^{16}$ and $NR^{15}SO_2R^{16}$

or

R^5 and R^6 together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring system optionally containing a further heteroatom selected from oxygen and nitrogen atoms, which ring is optionally substituted by 1, 2 or 3 substituents independently selected from phenyl, $-OR^{14}$, $-COOR^{14}$, $-NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-SO_2R^{10}$, $-SONR^{15}R^{16}$, $NR^{15}SO_2R^{16}$ or C_{1-6}alkyl (optionally substituted by 1 or 2 substituents independently selected from halo, $-NR^{15}R^{16}$ and $-OR^{17}$ groups);

R^{10} is hydrogen or a group selected from C_{1-6}alkyl or phenyl, wherein the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, phenyl, $-OR^{17}$ and $-NR^{15}R^{16}$; and each of R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14} R^{15}, R^{16}, R^{17} is independently hydrogen, C_{1-6}alkyl or phenyl;

R^x is trifluoromethyl, $-NR^5R^6$, phenyl, napthyl, monocyclic or bicyclic heteroaryl wherein a heteroring may be partially or fully saturated and one or more ring carbon atoms may form a carbonyl group, and wherein each phenyl or heteroaryl group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COR^7$,$-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_{1-6}alkyl or trifluoromethyl;;

or R^x is a group selected from C_{3-7}carbocyclyl, C_{1-8}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl whereby the group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COR^7$,$-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, phenyl or heteroaryl; and wherein each phenyl or heteroaryl group is optionally substituted by 1, 2 or 3 substituents independently selected from halo, cyano, nitro, $-OR^4$, $-NR^5R^6$, $-CONR^5R^6$, $-COR^7$,$-COOR^7$, $-NR^8COR^9$, $-SR^{10}$, $-SO_2R^{10}$, $-SO_2NR^5R^6$, $-NR^8SO_2R^9$, C_{1-6}alkyl or trifluoromethyl.

In particular Y is a bond; Y is -S-; Y is -O-; Y is $-NR^5$; Y is $-CF_2-CH_2-$; Y is $-CF_2CF_2-$; Y is $-CONR^5-$; Y is phenyl; or Y is heteroaryl.

Conveniently R^1 is benzyl or $-CH_2CH_2OPh$, or CH_2CH_2Ph where in each case the phenyl ring is optionally substituted by 1, 2 or 3 substituents independently selected from fluoro, chloro, bromo, methoxy, methyl and trifluoromethyl.

Conveniently R^2 is C_{1-8}alkyl optionally substituted by 1 or 2 hydroxy substituents and R^3 is hydrogen.

Conveniently R^x is methyl, trifluoromethyl, 1-methylimidazolyl, 1,2-dimethylimidazolyl, *N,N*-dimethylamino, azetidinyl, pyrolidinyl, morpholinyl or piperidinyl.

Certain compounds of formula (1) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (1) and mixtures thereof including racemates.

The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Within the present invention it is to be understood that a compound of formula (1) or a salt, solvate or *in vivo* hydrolysable ester thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form and mixtures thereof and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It is also to be understood that certain compounds of formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms.

The present invention relates to the compounds of formula (1) as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (1) and their pharmaceutically acceptable salts. Pharmaceutically

acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula (1) as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. Suitable salts include hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates, tartrates, oxalates, methanesulphonates or *p*-toluenesulphonates. Pharmaceutically acceptable salts of the invention may also include basic addition salts of the compounds of formula (1) as hereinbefore defined which are sufficiently acidic to form such salts. Such salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a lithium, sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or an organic amine salt, for example a salt with methylamine, dimethylamine, trimethylamine, triethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine. Other basic addition salts include aluminium, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine.

The present invention further relates to an *in vivo* hydrolysable ester of a compound of formula (1). An *in vivo* hydrolysable ester of a compound of formula (1) which contains carboxy or hydroxy group is, for example a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid or alcohol. Such esters can be identified by administering, for example, intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluid.

Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in-vivo* hydrolysable ester forming groups for hydroxy include C_{1-10}alkanoyl, for example acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, C_{1-10}alkoxycarbonyl (to give alkyl carbonate esters), for example ethoxycarbonyl; di-(C_{1-4})alkylcarbamoyl and *N*-(di-(C_{1-4})alkylaminoethyl)-*N*-(C_{1-4})alkylcarbamoyl (to give carbamates); di-(C_{1-4})alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, (C_{1-4})alkylaminomethyl and di-((C_{1-4})alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting in-vivo hyrolysable esters include, for example, $R^A C(O)O(C_{1-6})$alkyl-CO-, wherein R^A is for example, benzyloxy-(C_{1-4})alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-(C_{1-4})piperazino-(C_{1-4})alkyl, piperazino-(C_{1-4})alkyl and morpholino-(C_{1-4})alkyl.

In this specification the term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *t*-butyl are specific for the branched chain version only. For example, "C_{1-3}alkyl" includes methyl, ethyl, propyl and isopropyl and examples of "C_{1-6}alkyl" include the examples of "C_{1-3}alkyl"and additionally t-butyl, pentyl, 2,3-dimethylpropyl, 3-methylbutyl and hexyl. Examples of "C_{1-8}alkyl" include the examples of "C_{1-6}alkyl" and additionally heptyl, 2,3-dimethylpentyl, 1-propylbutyl and octyl. An analogous convention applies to other terms, for example "C_{2-6}alkenyl" includes vinyl, allyl, 1-propenyl , 2-butenyl, 3-butenyl, 3-methylbut-1-enyl, 1-pentenyl and 4-hexenyl and examples of "C_{2-6}alkynyl" includes ethynyl, 1-propynyl, 3-butynyl, 2-pentynyl and 1-methylpent-2-ynyl.

"C_{3-7}carbocyclyl" is a saturated, partially saturated or unsaturated, monocyclic ring containing 3 to 7 carbon ring atoms wherein a -CH_2- group can optionally be replaced by a -C(O)-. Suitable examples of "carbocyclyl" are cyclopropyl, cyclopentyl, cyclobutyl, cyclohexyl, cyclohexenyl, 4-oxocyclohex-1-yl and 3-oxocyclohept-5-en-1-yl.

The term "halo" refers to fluoro, chloro, bromo and iodo.

Examples of "C_{1-6}alkoxy" include methoxy, ethoxy, propoxy, isopropoxy, butyloxy, pentyloxy, 1-ethylpropoxy and hexyloxy. Examples of "C_{1-6}alkylamino" include methylamino, ethylamino, propylamino, butylamino and 2-methylpropylmino. Examples of "di(C_{1-6}alkyl)amino" include dimethylamino, *N*-methyl-*N*-ethylamino, diethylamino, *N*-propyl-*N*-3-methylbutylamino. Examples of "*N*-(C_{1-6}alkyl)-*N*-(phenyl)amino" include *N*-methyl-*N*-phenylamino, *N*-propyl-*N*-phenylamino and *N*-(2-methylbutyl)-*N*-phenylamino. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" are *N*-methylcarbamoyl, *N*-ethylcarbamoyl and *N*-(2-ethylbutylcarbamoyl. Examples of "*N*-(C_{1-6}alkyl)-*N*-(phenyl)carbamoyl" include *N*-methyl-*N*-phenylcarbamoyl, *N*-butyl-*N*-phenylcarbamoyl and *N*-(3-methylpentyl)-*N*-(phenyl)carbamoyl. Examples of "*N,N*-di(C_{1-6}alkyl)carbamoyl" include *N,N*-dimethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl and *N*-propyl-*N*-(2-methylbutyl)carbamoyl. Examples of "C_{1-6}alkylthio" include methylthio, ethylthio, propylthio, butylthio and 2-methylbutylthio.

"Heteroaryl" is a monocyclic or bicyclic aryl ring containing 5 to 10 ring atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen. Examples of heteroaryl include pyrrolyl, furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, benzfuranyl, benzthieno, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, benztriazolyl, quinolinyl, isoquinolinyl and naphthiridinyl. Conveniently heteroaryl is selected from imidazolyl, pyrazolyl, thiazolyl, isoxazolyl, furanyl, thienyl, isoxazolyl, or indazolyl.

Examples of "a 3-8 membered ring optionally containing 1, 2 or 3 atoms selected from O, S and NR^8" include oxetanyl, azetidinyl, benzodiazolyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, homopiperidinyl and homopiperazinyl tetrahydrodioxanyl., such as oxetanyl, azetidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, homopiperidinyl and homopiperazinyl, further such as pyrrolidinyl, tetrahydropyridinyl, piperidinyl, piperazinyl, and morpholinyl.

Examples of "a 4- to 7-membered saturated heterocyclic ring system" include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, homopiperazinyl and morpholinyl.

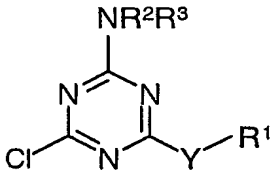
Where optional substituents are chosen from "1, 2 or 3" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups. An analogous convention applies to substituents chosen from "1 or 2" groups.

Particular compounds of the invention include *N*-[4-[[(2,3-difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-1,3,5-triazin-2-yl]-methanesulfonamide; *N*-[4-[[(2,3-difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-1,3,5-triazin-2-yl]-1-azetidinesulfonamide *N*-[4-[[(2,3-difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-1,3,5-triazin-2-yl]-methanesulfonamide *N*-[4-[[(2,3-difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-1,3,5-triazin-2-yl]-1-azetidinesulfonamide 4-morpholinesulfonamide, *N*-[4-[[(2,3-difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-1,3,5-triazin-2-yl]-methanesulfonamide, *N*-[4-[[2-(2,3-difluorophenoxy)ethyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-1,3,5-triazin-2-yl]-methanesulfonamide, 1,1,1-trifluoro-*N*-[4-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-6-(2-phenylethyl)-1,3,5-triazin-2-yl]- and pharmaceutically acceptable salts, solvates or *in vivo* hydrolysable esters thereof.

Each of the above mentioned compounds and the pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, individually is a particular aspect of the invention.

The present invention further provides a process for the preparation of compounds of formula (1) as defined above which comprises:

(a) treating a compound of formula (2):



(2)

wherein Y, R^1, R^2 and R^3 are as defined in formula (1) with sulfonamides ($R^xSO_2NH_2$) where R^x is as defined in formula (1).

and optionally thereafter (i), (ii), (iii), (iv), or (v) in any order:

i) removing any protecting groups;

ii) converting the compound of formula (1) into a further compound of formula (1)

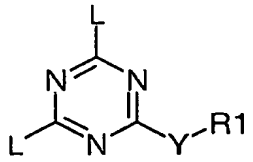
iii) forming a salt

iv) forming a prodrug

v) forming an *in vivo* hydrolysable ester.

Reaction of compounds of formula (2) wherein Y, R^1, R^2 and R^3 are as defined in formula (1) with sulfonamides ($R^xSO_2NH_2$) can be carried out in the presence of a suitable base, solvent and catalyst. Examples of suitable bases include metal carbonates such as those from ceasium, potassium, lithium or sodium. Most preferably ceasium carbonate is used. Suitable solvents include ethers such as tetrahydrofuran, 1,4-dioxane, glyme and diglyme. Preferably 1,4-dioxane is used. The temperature of the reaction can be performed between 10°C and 120°C, preferably at 100°C. Examples of suitable catalysts include a suitable palladium(0) source such as palladium tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$), or tetrakistriphenylphosphine ($Pd(Ph_3)_4$) (either in 0.01-0.5 mol equivalents) in the presence of a suitable ligand such as (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis[diphenyl-phosphine (Xantphos), or 2-dicyclohexyl-phosphino-2'-(N,N-dimethylamino)biphenyl (either in 0.01-0.5 mol equivalents). Preferably the catalyst combination is tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) with 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) in 0.01-0.5 mol equivalents in 1,4-dioxane at 100°C with ceasium carbonate as the base.

Compounds of formula (2) wherein Y, R^1, R^2 and R^3 are as defined in formula (1), can be prepared from compounds of formula (3) wherein R^1 are as defined in formula (1) and L is halogen by treatment with nucleophilic amines NR^2R^3 as defined in formula (1) in the presence of a suitable base and solvent.



(3)

Examples of suitable bases include trialkylamines, such as triethylamine or *N,N*-diisopropylethylamine. Suitable solvents include ethers such as tetrahydrofuran, 1,4-dioxane, glyme and diglyme. The temperature of the reaction can be performed between 0°C and 50°C. Preferably tetrahydrofuran is used at ambient temperature.

Compounds of formula (3) wherein Y is –S- and R^1 is as defined in formula (1) and L is halogen may be prepared by treating cyanuric chloride with a thiol of formula R^1SH

wherein R^1 is defined as in formula (1) in presence of a suitable base and solvent.. Suitable solvent include ethers such as tetrahydrofuran, 1,4-dioxane, glyme and diglyme. Suitable bases include trialkylamines, such as triethylamine or *N,N*-diisopropylethylamine. Preferably *N,N*-diisopropylethylamine is used as a base and tetrahydrofuran as the solvent is used at ambient temperature.

Compounds of formula (3) wherein Y is a bond and R^1 is as defined in formula (1) and L is halogen may be prepared by treating cyanuric chloride with a suitable Grignard reagent for example of formula $R^1(CH_2)_nMgL$ wherein L is a halogen and R^1 is defined as in formula (1) in presence of a suitable solvent such tetrahydrofuran or 1,4-dioxane. Preferably tetrahydrofuran at ambient temperature is used.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (1) may involve, at an appropriate stage, the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T. W. Greene & P. G. M. Wuts, Wiley–Interscience (1991).

A compound of formula (1) may be prepared from another compound of formula (1) by chemical modification. Examples of chemical modifications include standard alkylation, arylation, heteroarylation, acylation, sulphonylation, phosphorylation, aromatic halogenation and coupling reactions. These reactions may be used to add new substituents or to modify existing substituents. Alternatively, existing substituents in compounds of formula (1) may be modified by, for example, oxidation, reduction, elimination, hydrolysis or other cleavage reactions to yield other compounds of formula (1).

Novel intermediate compounds form a further aspect of the invention.

The compounds of formula (1) above may be converted to a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as discussed above. The salt is preferably a basic addition salt.

The compounds of formula (1) have activity as pharmaceuticals, in particular as modulators of chemokine receptor activity, such as for example CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and

CX_3CR1 for the C-X_3-C family; and especially as modulators of CXCR2 activity. Use of the compounds as modulators of each above mentioned receptor represents a separate and independent aspect of the invention.

The compounds of formula (1) may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of chemokines. Examples of such conditions/diseases include (each taken independently):

(1) **the respiratory tract** - obstructive airways diseases including chronic obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **bone and joints** - rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behchet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **skin** - psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

(4) **gastrointestinal tract** - Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, indeterminate colitis, microscopic colitis, inflammatory bowel disease, irritable bowel syndrome, non-inflammatory diarrhea, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **central and peripheral nervous system** - Neurodegenerative diseases and dementia disorders, e.g. Alzheimer's disease, amyotrophic lateral sclerosis and other motor neuron diseases, Creutzfeldt-Jacob's disease and other prion diseases,

HIV encephalopathy (AIDS dementia complex), Huntington's disease, frontotemporal dementia, Lewy body dementia and vascular dementia; polyneuropathies, e.g. Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, plexopathies; CNS demyelination, e.g. multiple sclerosis, acute disseminated/haemorrhagic encephalomyelitis, and subacute sclerosing panencephalitis; neuromuscular disorders, e.g. myasthenia gravis and Lambert-Eaton syndrome; spinal diorders, e.g. tropical spastic paraparesis, and stiff-man syndrome: paraneoplastic syndromes, e.g. cerebellar degeneration and encephalomyelitis; CNS trauma; migraine; and stroke.

(6) **other tissues and systemic disease** - atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, and idiopathic thrombocytopenia pupura; post-operative adhesions, and sepsis.

(7) **allograft rejection** - acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(8) **cancers** - especially non-small cell lung cancer (NSCLC), malignant melanoma, prostate cancer and squamous sarcoma, and tumour metastasis, non melanoma skin cancer and chemoprevention metastases;

(9) **diseases** - in which angiogenesis is associated with raised CXCR2 chemokine levels (e.g. NSCLC, diabetic retinopathy);

(10) **cystic fibrosis**;

(11) **burn wounds & chronic skin ulcers**;

(12) **reproductive diseases** – for example disorders of ovulation, menstruation and implantation, pre-term labour, endometriosis;

(13) **re-perfusion injury** - in the heart, brain, peripheral limbs and other organs, inhibition of atherosclerosis.

Thus, the present invention provides a compound of formula (1), or a pharmaceutically-acceptable salt, solvate or an *in vivo* hydrolysable ester thereof, as hereinbefore defined for use in therapy.

Preferably the compounds of the invention are used to treat diseases in which the chemokine receptor belongs to the CXC chemokine receptor subfamily, more preferably the target chemokine receptor is the CXCR2 receptor.

Particular conditions which can be treated with the compounds of the invention are cancer, diseases in which angiogenesis is associated with raised CXCR2 chemokine levels, and inflammatory diseases such as asthma, allergic rhinitis, COPD, rheumatoid arthritis, psoriasis, inflammatory bowel diseases, osteoarthritis or osteoporosis.

As a further aspect of the present invention, certain compounds of formula (1) may have utility as antagonists of the CX3CR1 receptor. Such compounds are expected to be particularly useful in the treatment of disorders within the central and peripheral nervous system and other conditions characterized by an activation of microglia and/or infiltration of leukocytes (e.g. stroke/ischemia and head trauma).

In a further aspect, the present invention provides a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined for use as a medicament.

In a still further aspect, the present invention provides the use of a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined for use as a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial.

In a still further aspect, the present invention provides the use of a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined for use as a medicament for the treatment of asthma, allergic rhinitis, cancer, COPD, rheumatoid arthritis, psoriasis, inflammatory bowel diseases, osteoarthritis or osteoporosis.

In a further aspect, the present invention provides the use of a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a still further aspect, the present invention provides the use of a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial.

In a still further aspect, the present invention provides the use of a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of asthma, allergic rhinitis, cancer, COPD, rheumatoid arthritis, psoriasis, inflammatory bowel diseases, osteoarthritis or osteoporosis.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating a chemokine mediated disease wherein the chemokine binds to a chemokine (especially CXCR2) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula , or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester, as hereinbefore defined.

The invention also provides a method of treating an inflammatory disease, especially asthma, allergic rhinitis, COPD, rheumatoid arthritis, psoriasis, inflammatory bowel diseases, osteoarthritis or osteoporosis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compounds of formula (1) and pharmaceutically acceptable salts, solvates or in vivo hydrolysable esters thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which formula (1) compound/salt/solvate/ester (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0:05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo*

hydrolysable ester thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (1), or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier. The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compounds of the invention are administered orally.

In addition to their use as therapeutic medicines, the compounds of formula (1) and their pharmaceutically acceptable salts, solvate or *in vivo* hydrolysable esters are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effect of chemokine modulation activity in labatory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

The invention further relates to combination therapies wherein a compound of formula (1) or a pharmaceutically acceptable salts, solvate or *in vivo* hydrolysable ester thereof, or a pharmaceutical composition or formulation comprising a compound of formula (1) is administered concurrently or sequentially with therapy and/or an agent for the treatment of any one of asthma, allergic rhinitis, cancer, COPD, rheumatoid arthritis, psoriasis, inflammatory bowel disease, irritable bowel syndrome, osteoarthritis or osteoporosis.

In particular, for the treatment of the inflammatory diseases rheumatoid arthritis, psoriasis, inflammatory bowel disease, irritable bowel syndrome, COPD, asthma and allergic rhinitis the compounds of the invention may be combined with agents such as TNF-α inhibitors such as anti-TNF monoclonal antibodies (such as Remicade, CDP-870 and D.sub2.E.sub7.) and TNF receptor immunoglobulin molecules (such as Enbrel.reg.), non-selective COX-1 / COX-2 inhibitors (such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin), COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib and

etoricoxib) low dose methotrexate, lefunomide; ciclesonide; hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold. For inflammatory bowel disease and irritable bowel disorder further convenient agents include sulphasalazine and 5-ASAs, topical and systemic steroids, immunomodulators and immunosuppressants, antibiotics, probiotics and anti-integrins.

The present invention still further relates to the combination of a compound of the invention together with a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; N-(5-substituted)-thiophene-2-alkylsulfonamides; 2,6-di-tert-butylphenol hydrazones; methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; pyridinyl-substituted 2-cyanonaphthalene compounds such as L-739,010; 2-cyanoquinoline compounds such as L-746,530; indole and quinoline compounds such as MK-591, MK-886, and BAY x 1005.

The present invention still further relates to the combination of a compound of the invention together with a receptor antagonist for leukotrienes LTB.sub4., LTC.sub4., LTD.sub4., and LTE.sub4. selected from the group consisting of the phenothiazin-3-ones such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention together with a PDE4 inhibitor including inhibitors of the isoform PDE4D.

The present invention still further relates to the combination of a compound of the invention together with a antihistaminic H.sub1. receptor antagonists such as cetirizine, loratadine, desloratadine, fexofenadine, astemizole, azelastine, and chlorpheniramine.

The present invention still further relates to the combination of a compound of the invention together with a gastroprotective H.sub2. receptor antagonist.

The present invention still further relates to the combination of a compound of the invention together with an α.sub1.- and α.sub2.-adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, and ethylnorepinephrine hydrochloride.

The present invention still further relates to the combination of a compound of the invention together with anticholinergic agents such as ipratropium bromide; tiotropium bromide; oxitropium bromide; pirenzepine; and telenzepine.

The present invention still further relates to the combination of a compound of the invention together with a β.sub1.- to β.sub4.-adrenoceptor agonists such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol; or methylxanthanines including theophylline and aminophylline; sodium cromoglycate; or muscarinic receptor (M1, M2, and M3) antagonist.

The present invention still further relates to the combination of a compound of the invention together with an insulin-like growth factor type I (IGF-1) mimetic.

The present invention still further relates to the combination of a compound of the invention together with an inhaled glucocorticoid with reduced systemic side effects, such as prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate.

The present invention still further relates to the combination of.a compound of the invention together with an inhibitor of matrix metalloproteases (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-12.

The present invention still further relates to the combination of a compound of the invention together with other modulators of chemokine receptor function such as CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX_3CR1 for the C-X_3-C family.

The present invention still further relates to the combination of a compound of the invention together with antiviral agents such as Viracept, AZT, aciclovir and famciclovir, and antisepsis compounds such as Valant.

The present invention still further relates to the combination of a compound of the invention together with cardiovascular agents such as calcium channel blockers, lipid lowering agents such as statins, fibrates, beta-blockers, Ace inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

The present invention still further relates to the combination of a compound of the invention together with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

The present invention still further relates to the combination of a compound of the invention together with (i) tryptase inhibitors; (ii) platelet activating factor (PAF) antagonists; (iii) interleukin converting enzyme (ICE) inhibitors; (iv) IMPDH inhibitors; (v) adhesion molecule inhibitors including VLA-4 antagonists; (vi) cathepsins; (vii) MAP kinase inhibitors; (viii) glucose-6 phosphate dehydrogenase inhibitors; (ix) kinin-B.sub1. - and B.sub2. -receptor antagonists; (x) anti-gout agents, e.g., colchicine; (xi) xanthine oxidase inhibitors, e.g., allopurinol; (xii) uricosuric agents, e.g., probenecid, sulfinpyrazone, and benzbromarone; (xiii) growth hormone secretagogues; (xiv) transforming growth factor (TGFβ); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor, e.g., basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) Tachykinin NK.sub1. and NK.sub3. receptor antagonists selected from the group consisting of NKP-608C; SB-233412 (talnetant); and D-4418; (xx) elastase inhibitors selected from the group consisting of UT-77 and ZD-0892; (xxi) TNFδ converting enzyme inhibitors (TACE); (xxii) induced nitric oxide synthase inhibitors (iNOS) or (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (CRTH2 antagonists).

The compounds of the present invention may also be used in combination with osteoporosis agents such as roloxifene, droloxifene, lasofoxifene or fosomax and immunosuppressant agents such as FK-506, rapamycin, cyclosporine, azathioprine, and methotrexate;.

The compounds of the invention may also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors

such as celecoxib, valdecoxib, rofecoxib and etoricoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc and P2X7 receptor antagonists.

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of cancer. Suitable agents to be used in combination include:

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine and paclitaxel (Taxol®); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) Agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]) , farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-

4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Pharmacological Data

Ligand Binding Assay

[^{125}I]IL-8 (human, recombinant) was purchased from Amersham, U.K. with a specific activity of 2,000Ci/mmol. All other chemicals were of analytical grade. High levels of hrCXCR2 were expressed in HEK 293 cells (human embryo kidney 293 cells ECACC No. 85120602) (Lee *et al.* (1992) *J. Biol. Chem.* **267** pp16283-16291). hrCXCR2 cDNA was amplified and cloned from human neutrophil mRNA. The DNA was cloned into PCRScript (Stratagene) and clones were identified using DNA. The coding sequence was sub-cloned into the eukaryotic

expression vector RcCMV (Invitrogen). Plasmid DNA was prepared using Quiagen Megaprep 2500 and transfected into HEK 293 cells using Lipofectamine reagent (Gibco BRL). Cells of the highest expressing clone were harvested in phosphate-buffered saline containing 0.2%(w/v) ethylenediaminetetraacetic acid (EDTA) and centrifuged (200g, 5min.). The cell pellet was resuspended in ice cold homogenisation buffer [10mM HEPES (pH 7.4), 1mM dithiothreitol, 1mM EDTA and a panel of protease inhibitors (1mM phenyl methyl sulphonyl fluoride, 2μg/ml soybean trypsin inhibitor, 3mM benzamidine, 0.5μg/ml leupeptin and 100μg/ml bacitracin)] and the cells left to swell for 10 minutes. The cell preparation was disrupted using a hand held glass mortar/PTFE pestle homogeniser and cell membranes harvested by centrifugation (45 minutes, 100,000g, 4°C). The membrane preparation was stored at -70°C in homogenisation buffer supplemented with Tyrode's salt solution (137mM NaCl, 2.7mM KCl, 0.4mM NaH_2PO_4), 0.1%(w/v) gelatin and 10%(v/v) glycerol.

All assays were performed in a 96-well MultiScreen 0.45μm filtration plates (Millipore, U.K.). Each assay contained ~50pM [^{125}I]IL-8 and membranes (equivalent to ~200,000 cells) in assay buffer [Tyrode's salt solution supplemented with 10mM HEPES (pH 7.4), 1.8mM $CaCl_2$, 1mM $MgCl_2$, 0.125mg/ml bacitracin and 0.1%(w/v) gelatin]. In addition, a compound of formula (I) according to the Examples was pre-dissolved in DMSO and added to reach a final concentration of 1%(v/v) DMSO. The assay was initiated with the addition of membranes and after 1.5 hours at room temperature the membranes were harvested by filtration using a Millipore MultiScreen vacuum manifold and washed twice with assay buffer (without bacitracin). The backing plate was removed from the MultiScreen plate assembly, the filters dried at room temperature, punched out and then counted on a Cobra gamma-counter.

The compounds of formula (I) according to the Examples 1 – 7 were found to have pIC_{50} values of greater than (>) 5.0.

Intracellular Calcium Mobilisation Assay

Human neutrophils were prepared from EDTA-treated peripheral blood, as previously described (Baly *et al.* (1997) Methods in Enzymology 287 pp70-72), in storage buffer [Tyrode's salt solution (137mM NaCl, 2.7mM KCl, 0.4mM NaH_2PO_4) supplemented with 5.7mM glucose and 10mM HEPES (pH 7.4)].

The chemokine GROδ (human, recombinant) was purchased from R&D Systems (Abingdon, U.K.). All other chemicals were of analytical grade. Changes in intracellular free calcium were measured fluorometrically by loading neutrophils with the calcium sensitive

fluorescent dye, fluo-3, as described previously (Merritt *et al.* (1990) Biochem. J. 269, pp513-519). Cells were loaded for 1 hour at 37°C in lo ading buffer (storage buffer with 0.1%(w/v) gelatin) containing 5μM fluo-3 AM ester, washed with loading buffer and then resuspended in Tyrode's salt solution supplemented with 5.7mM glucose, 0.1%(w/v) bovine serum albumin (BSA), 1.8mM $CaCl_2$ and 1mM $MgCl_2$. The cells were pipetted into black walled, clear bottom, 96 well micro plates (Costar, Boston, U.S.A.) and centrifuged (200g, 5 minutes, room temperature).

A compound of formula (I) according to the Examples was pre-dissolved in DMSO and added to a final concentration of 0.1 %(v/v) DMSO. Assays were initiated by the addition of an A_{50} concentration of GROα and the transient increase in fluo-3 fluorescence (δ_{Ex} =490nm and δ_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

The compounds of formula (I) according to the Examples were tested and found to be antagonists of the CXCR2 receptor in human neutrophils.

The invention will now be illustrated by the following non-limiting Examples in which, unless stated otherwise:

(i) when given Nuclear Magnetic Resonance (NMR) spectra were measured on a Varian Unity Inova 300 or 400 MHz spectrometer. ^{1}H NMR data is quoted in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard.

(ii) Mass Spectrometry (MS) spectra were measured on a Finnigan Mat SSQ7000 or Micromass Platform spectrometer.

(iii) the title and sub-titled compounds of the Examples and methods were named using the ACD/Name program (version 4.55) from Advanced Chemical Development Inc, Canada.

(iv) Normal phase column chromatography and normal phase HPLC was conducted using a silica column. Reverse phase High Pressure Liquid Chromatography (HPLC) purification was performed using either a Waters Micromass LCZ with a Waters 600 pump controller, Waters 2487 detector and Gilson FC024 fraction collector or a Waters Delta Prep 4000 or a Gilson Auto Purification System, using a Symmetry, NovaPak or Ex-Terra reverse phase silica column.

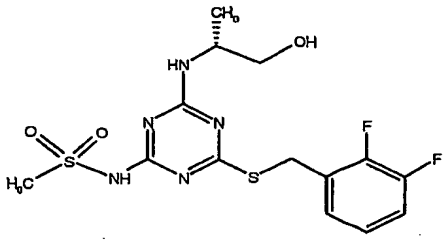
(v) The following abbreviations are used:

AcOH acetic acid

$CHCl_3$	chloroform
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
Et_2O	diethyl ether
EtOAc	ethyl acetate
$MgSO_4$	magnesium sulfate
NMP	1-methylpyrrolidin-2-one
THF	tetrahydrofuran
H_2O	water

Example 1

***N*-[4-[[(2,3-difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-1,3,5-triazin-2-yl]-methanesulfonamide**



A mixture of methane sulphonamide (0.17 g), tris(dibenzylideneacetone)dipalladium (0) (13 mg), (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis[diphenyl-phosphine (8 mg) and cesium carbonate were stirred under a nitrogen atmosphere for 5 minutes. A solution of 2-[[4-chloro-6-[[(2,3-difluorophenyl)methyl]thio]-1,3,5-triazin-2-yl]amino]-(2*R*)-1-propanol (0.5 g) in anhydrous 1,4-dioxane (5 ml) was added to the above mixture and the reaction was heated to reflux in a pre-heated heat on block for 25 minutes. The reaction mixture was allowed to cool to ambient temperature, diluted with 1N aqueous hydrochloric acid solution and extracted with ethyl acetate (x3). The combined organic layers were dried with magnesium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica using a 99:1 to 98:2 mixture of methylene chloride and methanol as eluent. The resulting solid was further purified by reverse phase HPLC using a 95:5 to 5:95 mixture of 0.2% aqueous ammonium acetate solution and acetonitrile as eluent to give the title compound as a white solid (0.3 g).

NMR Spectrum: (CD_3OD) δ 1.21 (m, 3H), 3.33 (m, 3H), 3.58 (m, 2H), 4.19 (m, 1H), 4.56 (m, 2H), 7.16 (m, 2H), 7.38 (m, 1H);

Mass Spectrum: $M+H^+$ 406;

Elemental Analysis: Found C, 40.05; H, 4.80; N, 16.48; $C_{14}H_{17}F_2N_5O_3S_2.1H_2O$ requires C, 39.71; H, 4.52; N, 16.54%.

The 2-[[4-chloro-6-[[(2,3-difluorophenyl)methyl]thio]-1,3,5-triazin-2-yl]amino]-(2*R*)-1-propanol used as a starting material was prepared as follows :-

i) (2,3-difluorophenyl)methanethiol

Thiourea (6.7 g) was added to a stirred solution of 2,3-difluorobenzylbromide (18.3 g), in ethanol (300 ml). The reaction mixture was heated at reflux for 2.5 hours and then evaporated, treated with 2N sodium hydroxide solution (440 ml) and heated at reflux for a

further 4 hours and left stirring at ambient temperature overnight. The resulting mixture was ice-cooled, acidified to pH 6 using concentrated aqueous hydrochloric acid solution and then extracted with diethyl ether. The organic layer was separated, washed with water, dried over anhydrous magnesium sulphate, filtered and evaporated to give (2,3-difluorophenyl)methanethiol (8.0 g). NMR Spectrum: ($CDCl_3$) δ 1.90 (t, 1H), 3.78 (d, 2H), 7.06 (m, 3H).

ii) 2-[[4-chloro-6-[[(2,3-difluorophenyl)methyl]thio]-1,3,5-triazin-2-yl]amino]-(2*R*)- 1-propanol

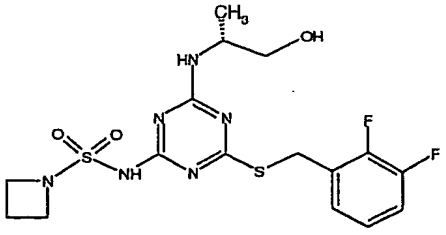
To an ice-bath cooled solution of cyanuric chloride (3.0 g) and diisopropylethlamine (3.1 ml) in anhydrous tetrahydrofuran (100 ml) was added a solution of (2,3-difluorophenyl)methanethiol (2.6 g) dropwise over 30 minutes. The reaction mixture was stirred at 0°C under a nitrogen atmosphere for 40 minutes. Further diisopropylethlamine (3.1 ml) was added, followed by a solution of R-(D)-alaninol (1.2 g) in anhydrous tetrahydrofuran (20 ml) dropwise over 5 minutes. The resulting reaction mixture was stirred at 0°C under a nitrogen atmosphere for 55 minutes. The mixture was diluted with brine and extracted with ethyl acetate (x2). The combined organic layers were dried with magnesium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica using a 90:10 to 70:30 to 60:40 mixture of iso-hexane and ethylacetate as eluent to give 2-[[4-chloro-6-[[(2,3-difluorophenyl)methyl]thio]-1,3,5-triazin-2-yl]amino]-(2*R*)- 1-propanol as a white solid (5.1 g).

NMR Spectrum: (DMSO) δ 1.16 (m, 3H), 3.37 (m, 2H), 4.02 (m, 1H), 4.43 (m, 2H), 4.76 (m, 1H), 7.16 (m, 1H), 7.38 (m, 2H), 8.49 (t, 1H);

Mass Spectrum: $M+H^+$ 347/349

Example 2

***N*-[4-[[(2,3-difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-1,3,5-triazin-2-yl]-1-azetidinesulfonamide**



Prepared using the same procedure as for the title compound in example 1; from 2-[[4-chloro-6-[[(2,3-difluorophenyl)methyl]thio]-1,3,5-triazin-2-yl]amino]-(2*R*)-1-propanol (0.5 g) and azetadine-1-sulfonamide (0.25g) to give the title compound as a white solid (120 mg).

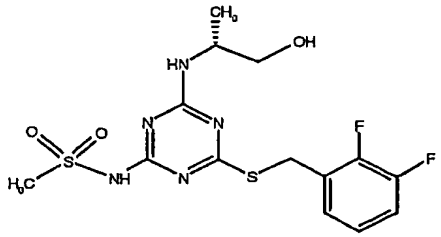
NMR Spectrum: (CD_3OD) δ 1.18 (m, 3H), 2.17 (quintet, 2H), 3.55 (m, 2H), 4.06 (t, 4H), 4.16 (m, 1H), 4.43 (m, 2H), 7.12 (m, 2H), 7.37 (m, 1H);

Mass Spectrum: $M+H^+$ 447;

Elemental Analysis: Found C, 42.52; H, 4.86; N, 17.68; $C_{16}H_{20}F_2N_6O_3S_2.0.3H_2O$. 0.3AcOH requires C, 42.43; H, 4.68; N, 17.88%.

Example 3

***N*-[4-[[(2,3-difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-1,3,5-triazin-2-yl]-methanesulfonamide**



A mixture of methane sulphonamide (0.17 g), tris(dibenzylideneacetone)dipalladium (0) (13 mg), (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis[diphenyl-phosphine (8 mg) and cesium carbonate were stirred under a nitrogen atmosphere for 5 minutes. A solution of 2-[[4-chloro-6-[[(2,3-difluorophenyl)methyl]thio]-1,3,5-triazin-2-yl]amino]-(2*R*)-1-propanol (0.5 g) in anhydrous 1,4-dioxane (5 ml) was added to the above mixture and the reaction was heated to reflux in a pre-heated heat on block for 25 minutes. The reaction mixture was allowed to cool to ambient temperature, diluted with 1N aqueous hydrochloric acid solution and extracted with ethyl acetate (x3). The combined organic layers were dried with magnesium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica using a 99:1 to 98:2 mixture of methylene chloride and methanol as eluent. The resulting solid was further purified by reverse phase HPLC using a 95:5 to 5:95 mixture of 0.2% aqueous ammonium acetate solution and acetonitrile as eluent to give the title compound as a white solid (0.3 g).

Mass Spectrum: [$M+H^+$] 406

NMR Spectrum: (CD_3OD) δ:1.21 (m, 3H), 3.33 (m, 3H), 3.58 (m, 2H), 4.19 (m, 1H), 4.56 (m, 2H), 7.16 (m, 2H), 7.38 (m, 1H);

The 2-[[4-chloro-6-[[(2,3-difluorophenyl)methyl]thio]-1,3,5-triazin-2-yl]amino]-(2*R*)-1-propanol used as a starting material was prepared as follows :-

i) (2,3-difluorophenyl)methanethiol

Thiourea (6.7 g) was added to a stirred solution of 2,3-difluorobenzylbromide (18.3 g), in ethanol (300 ml). The reaction mixture was heated at reflux for 2.5 hours and then evaporated, treated with 2N sodium hydroxide solution (440 ml) and heated at reflux for a further 4 hours and left stirring at ambient temperature overnight. The resulting mixture was ice-cooled, acidified to pH 6 using concentrated aqueous hydrochloric acid solution and then extracted with diethyl ether. The organic layer was separated, washed with water, dried over anhydrous magnesium sulphate, filtered and evaporated to give the subtitle compound as an oil. (8.0 g).

NMR Spectrum: ($CDCl_3$) δ: 1.90 (t, 1H), 3.78 (d, 2H), 7.06 (m, 3H).

ii) (2*R*)-2-[[4-chloro-6-[[(2,3-difluorophenyl)methyl]thio]-1,3,5-triazin-2-yl]amino]-1-propanol

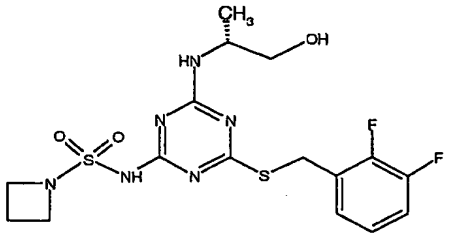
To an ice-bath cooled solution of cyanuric chloride (3.0 g) and N,N-diisopropylethlamine (3.1 ml) in anhydrous tetrahydrofuran (100 ml) was added a solution of the product of step (i) (2.6 g) dropwise over 30 minutes. The reaction mixture was stirred at 0°C under a nitrogen atmosphere for 40 minutes. Further N,N-diisopropylethlamine (3.1 ml) was added, followed by a solution of R-(D)-alaninol (1.2 g) in anhydrous tetrahydrofuran (20 ml) dropwise over 5 minutes. The resulting reaction mixture was stirred at 0°C under a nitrogen atmosphere for 55 minutes. The mixture was diluted with brine and extracted with ethyl acetate twice. The combined organic layers were dried with magnesium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica using a 90:10 to 70:30 to 60:40 mixture of iso-hexane and ethylacetate as eluent to give subtitle compound as a white solid (5.1g).

Mass Spectrum: [$M+H^+$] 347/349

NMR Spectrum: (DMSO) δ: 1.16 (m, 3H), 3.37 (m, 2H), 4.02 (m, 1H), 4.43 (m, 2H), 4.76 (m, 1H), 7.16 (m, 1H), 7.38 (m, 2H), 8.49 (t, 1H);

Example 4

***N*-[4-[[(2,3-difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-1,3,5-triazin-2-yl]-1-azetidinesulfonamide**



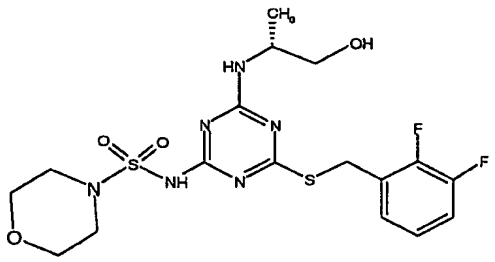
Prepared using the same procedure as for the title compound in example 1; from 2-[[4-chloro-6-[[(2,3-difluorophenyl)methyl]thio]-1,3,5-triazin-2-yl]amino]-(2*R*)-1-propanol (0.5 g) and azetadine-1-sulfonamide (0.25g) to give the title compound as a white solid (120 mg).

Mass Spectrum: $[M+H^+]$ 447

NMR Spectrum: $(CD_3OD)\delta$: 1.18 (m, 3H), 2.17 (quintet, 2H), 3.55 (m, 2H), 4.06 (t, 4H), 4.16 (m, 1H), 4.43 (m, 2H), 7.12 (m, 2H), 7.37 (m, 1H);

Example 5

4-morpholinesulfonamide, *N*-[4-[[(2,3-difluorophenyl)methyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-1,3,5-triazin-2-yl]-



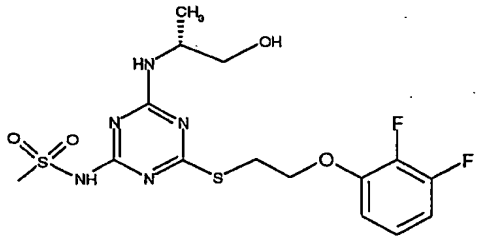
Prepared using the same procedure as for the title compound in example 1; from 2-[[4-chloro-6-[[(2,3-difluorophenyl)methyl]thio]-1,3,5-triazin-2-yl]amino]-(2*R*)-1-propanol (0.5g) and morpholine-1-sulfonamide (0.25g) to give the title compound as a white solid (290mg).

Mass Spectrum: $[M+H^+]$ 477

NMR Spectrum: (DMSO)δ: 1.09 (m, 3H), 3.24 (m, 4H), 3.37 (m, 2H), 3.58 (m, 4H), 4.03 (m, 1H), 4.41 (m, 2H), 4.75 (bs, 1H), 7.16 (m, 1H), 7.32 (m, 2H), 7.40-7.72 (m, 2H)

Example 6

methanesulfonamide, *N*-[4-[[2-(2,3-difluorophenoxy)ethyl]thio]-6-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-1,3,5-triazin-2-yl]-



Prepared using the same procedure as for the title compound in example 1; from (2*R*)-2-[[4-chloro-6-[[2-(2,3-difluorophenoxy)ethyl]thio]-1,3,5-triazin-2-yl]amino]- 1-propanol, (0.45g) and methanesulfonamide (0.14g) to give the title compound after purification by recystallisation from ethyl acetate as a white solid (250mg).

Mass Spectrum: $[M+H^+]$ 436

NMR Spectrum: $(CD_3OD)\delta$: 1.21(dd, 3H), 3.36(m, 3H), 3.54(m, 4H), 4.16(m, 1H), 4.34(m, 2H), 6.82(q, 1H), 6.94(t, 1H), 7.07(m, 1H)

The (2*R*)- 2-[[4-chloro-6-[[2-(2,3-difluorophenoxy)ethyl]thio]-1,3,5-triazin-2-yl]amino]-1-propanol used as a starting material was prepared as follows :-

(i) (2*R*)- 2-[[4-chloro-6-[[2-(2,3-difluorophenoxy)ethyl]thio]-1,3,5-triazin-2-yl]amino]-1-propanol

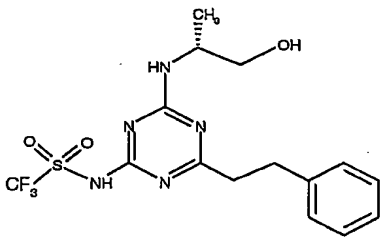
Prepared using the same procedure as for the title compound in example 1 step (ii) from cyanuric chloride (0.66g), 2-(2,3-difluorophenoxy)ethanethiol (0.68g), and R-(D)-alaninol (270mg) to give the title compound as a clear oil (0.9g).

Mass Spectrum: $[M+H^+]$ 377/379

NMR Spectrum: (DMSO) δ:1.07(dd, 3H), 3.37(m, 2H), 3.46(m, 2H), 3.97(m, 1H), 4.35(q, 2H), 4.76(m 1H), 7.02(m, 1H), 7.14(m 2H), 8.44(dd, 1H)

Example 7

methanesulfonamide, 1,1,1-trifluoro-*N*-[4-[[(1*R*)-2-hydroxy-1-methylethyl]amino]-6-(2-phenylethyl)-1,3,5-triazin-2-yl]-



Prepared using the same procedure as for the title compound in example 1; from (2*R*)- 2-[[4-chloro-6-(2-phenylethyl)-1,3,5-triazin-2-yl]amino]- 1-propanol (0.29g) and trifluoromethanesulfonamide (0.22g) to give the title compound after purification by reverse phase HPLC as a white solid (5mg).

Mass Spectrum: $[M+H^+]$ 406

NMR Spectrum: (CD_3OD) δ: 1.23(d, 3H), 2.81(t, 2H), 3.03(t, 2H), 3.65(dd, 1H), 3.63(dd, 1H), 4.20-4.27(m, 1H), 7.16-7.29(m, 5H)

The (2*R*)- 2-[[4-chloro-6-(2-phenylethyl)-1,3,5-triazin-2-yl]amino]- 1-propanol used as a starting material was prepared as follows :-

(i) (2*R*)- 2-[[4-chloro-6-(2-phenylethyl)-1,3,5-triazin-2-yl]amino]- 1-propanol

A solution of phenethyl bromide (1.82ml) in dry diethyl ether (12ml) was treated with magnesium turnings (0.3g) under nitrogen atmosphere with gentle warming until all the magnesium had reated to produce a solution of the Grignard reagent. This solution was then added dropwise to a solution of cyanuric chloride (1.84g) in benzene (10ml) at 0°C with stirring. After stirring at this temperature for 2h the mixture was allowed to warm to ambient temperature for a further 16h. The mixture was then treated with N,N-diisopropylethylamine (5.3ml) followed by R-(D)-alaninol (2.3ml) and the whole allowed to stir for a further 48h. The mixture was concentrated under vacuo and the residue partitioned between dichloromethane and water. The organic layer was collected and further washed with 2M

hydrochloric acid, saturated sodium bicarbonate solution and water again. The organic layer collected, dried ($MgSO_4$) and solvent evaporated to leave the subtitle product as an orange oil (3g). Mass Spectrum: $[M+H^+]$ 293.